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Case Report

A case of guilt by association: Water bug bite incriminated in *M. ulcerans* infection

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ABSTRACT

Buruli ulcer is a cutaneous mycobacterial disease caused by *Mycobacterium ulcerans*, whose incidence is increasing steadily, especially in West Africa. This study reports a first documented case of *M. ulcerans* infection which can be attributed to a water bug bite at the site of the primary lesion.

Introduction

Arthropod bites are common and are responsible for pathogen transmission to humans. Parasites causing malaria, leishmaniasis, and Chagas disease are transmitted by mosquitoes, sand flies and Triatominae, respectively. Lyme disease is caused by the bacterium Borrelia, transmitted to humans through the bite of infected ticks. Similarly, arthropods are vectors for various viruses, such as for those causing Dengue or the West Nile fever. In this general picture, it is then noticeable that an insect-mediated infection has been also consistently suspected in the case of Buruli ulcer, a skin infectious disease caused by *Mycobacterium ulcerans*, but not proven until now. Indeed, the reservoirs and modes of transmission of *M. ulcerans* to humans are still poorly characterized. In Buruli ulcer, classified as one of 13 neglected tropical diseases, after a period of incubation estimated to be from a few weeks to several months, the disease manifests

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as a painless nodule, a firm plaque or an edematous lesion which soon ulcerates [1].

Even though several insect models, including mosquitoes, have been considered for insect-mediated infection with *M. ulcerans*, it appears that water bugs of Belostomatidae and Naucoridae families may represent privileged candidates with this respect, based on a series of converging indices [2–12]. These insects belong to the order Hemiptera, familiar in a wide variety of aquatic habitats throughout the world. They are predacious fluid feeders, feeding on small vertebrates and aquatic invertebrates [13] and also known to have flying abilities, mainly at night time attracted by light. The involvement of water bugs in the transmission of *M. ulcerans* to humans was suggested by: (1) Belostomatidae and Naucoridae water bugs are able to bite humans while submerged in the aquatic environment or flying in the air, as a defense mechanism [13–14]; (2) it was shown in animal models that *M. ulcerans* could be transmitted to mice or insect larvae by inoculation following a bite from a water bug [6,7,15]; and (3) in an environmental study, viable and virulent *M. ulcerans* bacilli were detected in the saliva of Belostomatidae and Naucoridae specimens caught in a Buruli ulcer endemic area [2].

This study shows that indeed *M. ulcerans* can be transmitted to humans by insects, reporting the first documented case for such transmission. In this specific case, the contamination was through a bite by a water bug from the Belostomatidae family, demonstrating the ability of such insects to act as vectors for the transmission of *M. ulcerans* to humans.

Case report

A 6 year-old girl from Mowe (Ogun State, Nigeria) was brought to CDTUB-Pobe in Benin (Centre de Diagnostic et de Traitement de l'Ulcère de Buruli, Pobè, Republic of Benin) with an extensive swelling from the top of the left arm to the dorsum of the left hand which had been evolving for two months (Fig. 1A and B). The left arm showed only a small ulceration (Fig. 1C). The clinical picture was typical of *M. ulcerans* infection (Buruli ulcer). Diagnosis was confirmed by a Q-PCR analysis (as previously described by Rondini et al. [16]) of tissues obtained by fine-needle aspiration, from which *M. ulcerans* was grown onto Löwenstein-Jensen medium; however, Ziehl–Neelsen staining analysis was negative. The patient was otherwise healthy with normal routine laboratory results (Complete Blood Count), and radiological investigations failed to reveal bone involvement. Following the World Health Organization (WHO) recommendations, antibiotic treatment was administered for a period of 56 days (Rifampicin 10 mg/kg/day and streptomycin 15 mg/kg/day). Two weeks after the beginning of antibiotherapy, a significant decrease of oedema was observed and surgical excision was planned 4 weeks after the beginning of the treatment. Three months after starting chemotherapy, the patient was considered as cured.

During the first medical examination, the patient attributed the beginning of the lesion to the bite of an insect. The bite had occurred while the child was playing at nightfall in the vicinity of the canal, some 50 meters from her house. She was bitten painfully by a flying insect on the left arm at

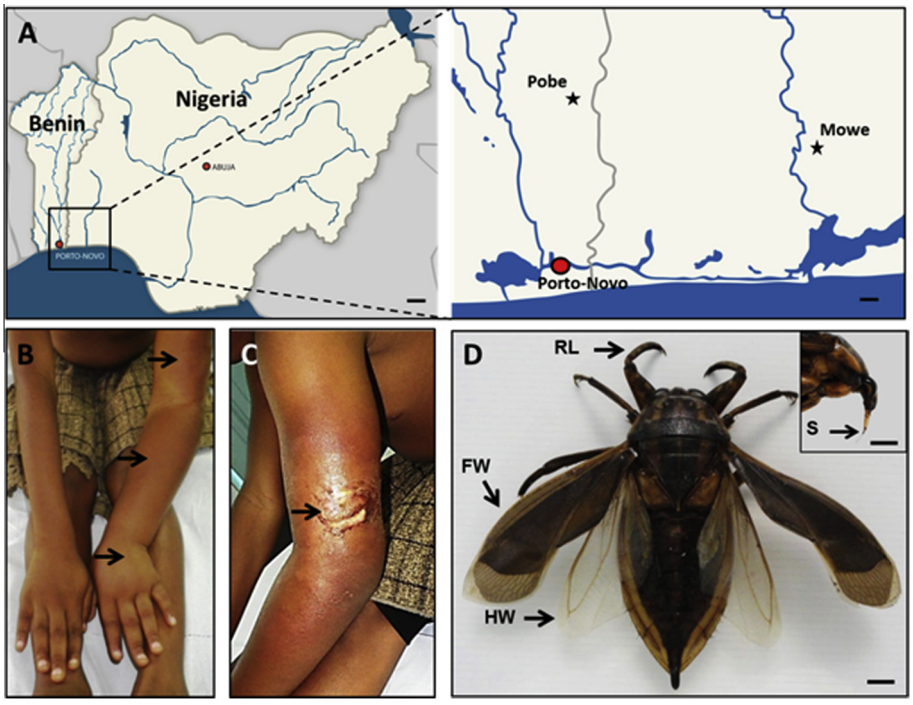

Fig. 1 – (A) Patient lives at Mowe city in Nigeria and was treated in CDTUB hospital at Pobe city, in Benin. (B) Patient presented with an extensive swelling (arrows) from the top of the left arm to the dorsum of the left hand. (C) Patient had an ulceration on the left arm (arrow). (D) Belostomatidae specimen was recognized by the patient as the flying insect which had bitten her left arm a few weeks before the lesion onset. (RL) Raptorial leg, (FW) Forewing, (HF) Hind wing (S) retractable stylet. Scales: (A) left map: 50 km, right map: 5 km. (D)1 cm, insert: 0.8 cm.

the actual location of the small ulcer visible at the time of examination (Fig. 1C). As reported by the girl and her mother, the bite originally caused a small skin lesion, which progressively evolved towards an oedema around the bite location after two weeks. In order to identify unambiguously the responsible insect, the medical staff organised an "identification parade", which included nine specimens of aquatic insects from coleoptera, hemiptera, odonata and lepidoptera orders. The girl identified at once the specimen belonging to the Belostomatidae family (a giant water bug specimen) (Fig. 1D) as the one which had bitten her. As a matter of fact, the clinical manifestations of the bite as reported by the girl and the mother, concerning notably the extreme painfulness and the apparition of the small skin lesion, were similar to those described previously in a study of bites caused by water bugs belonging to the Belostomatidae family [14]. However, as a major difference, in this previous study, the lesions healed in all the cases, without sequelae, whereas in this case, an oedema caused by *M. ulcerans* appeared progressively around the bite location after two weeks. Finally, the mother of the child further confirmed that she previously encountered this insect in water during the day time or flying in the air at night time. It was also important to note that the child was not exposed to daily contact with water from the river, as the family had unlimited access to drinkable water. To note, this medical team reported (between 2010 and 2013) several other Buruli ulcer patients associating their lesion development after a water bug bite.

Discussion

The occurrence of Buruli ulcer disease was mainly observed in low elevation areas, swamps or other marshy environments. It was then hypothesized early on that aquatic ecosystems can serve as important reservoirs for the transmission of *M. ulcerans* [17]. The exact modes of transmission of *M. ulcerans* to humans remain poorly characterized. Various mechanisms have been suggested for such transmission. Nonetheless, as reported for various environmental mycobacteria [18], the routes of transmission should involve the inoculation of bacilli into the host tissues. In this background, over the past decade, several studies consistently pointed towards the possible role of insects in *M. ulcerans* transmission [2,7,10,12,19], more specifically incriminating biting water bugs as hosts and vectors in such transmission [2,7,10,15]. Indeed, studies on mouse models demonstrated that *M. ulcerans,* transmitted through biting, was able to colonize the salivary glands of water bugs [2]. Field investigations further showed that the water bugs captured in endemic areas were colonized by *M. ulcerans*, in support of their role as vectors [2,10,20].

In the background above, a link was missing between the environmental hints and the clinical mouse studies to put forward a coherent model of *M. ulcerans* transmission to humans via various types of insect vectors. Concerning water bugs of the Belostomatidae family, the case report here fills in the gap between the environmental and animal studies for the completion of a model which can account for the full transmission cycle of *M. ulcerans* to humans: the salivary glands of water bugs can be colonized by *M. ulcerans* which can then be inoculated in the skin tissue via insect bites.

It may seem surprising that the missing gap could not be filled until now. It is, however, important to stress that the case reported here fulfilled several important requirements, which are rarely met together: (i) the bite was done outside a water environment; (ii) the biting insect was of large size (more than 4 cm), largely facilitating the unambiguous identification of the incriminated insect specimen; and (iii) the patient was brought early enough to the hospital, still having a vivid memory of the reported events.

Conclusions

The recognition and general acceptance of water bugs as vectors for the transmission of *M. ulcerans* to humans should provoke increasing awareness of the risks associated with bites from such insects, which could then have repercussionsrepercuted in the development of appropriate protection/supervision strategies.

Consent

Written informed consent was obtained from the mother of the patient for publication of this case report.

Conflict of interest

The authors have no conflict of interest to declare.

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